

95-325541/42 B02 KITA 94.02.15  
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 94.02.15 94JP-018612 (95.08.22) C07D 498/22 // A61K 31/52, 31/55  
 (C07D 209:00, 309:14, 498/22, 273:06) (C07D 209:00, 273:06, 498/22,  
 309:28) (C07D 209:00, 307:24, 498/22) (C07D 209:00, 309:10, 498/22,  
 273:06)  
 7-Alkoxy- or hydroxy-staurosporine deriv. prepn. in high yield -  
 from corresp. 7-unsubstituted staurosporine (II) with a lower alcohol in the  
 presence of a quinone oxidant in an inert solvent  
 C95-144522  
 Addnl. Data: ASAHI KASEI KOGYO KK (ASAHI)

Prepn. of a 7-alkoxy-staurosporine deriv. (I) contg. a subst. tetrahydropyran or tetrahydrofuran ring comprises reacting the corresp. 7-unsubstituted staurosporine (II) with a lower alcohol in the presence of a quinone oxidant in an inert solvent.

The obtd. (I) is opt. hydrolysed in presence of acid catalyst to give the corresp. 7-hydroxy-staurosporine deriv. (I') contg. a subst. tetrahydropyran or tetrahydrofuran ring.

#### USE

(I) and (I') have various biological activities based on protein kinase C inhibition.

B(6-E5, 14-D6) .2

#### ADVANTAGE

The method gives a high yield without using heavy metal oxidants (such as lead tetraacetate), and is industrially applicable.

#### OXIDANT

2,3-Dichloro-5,6-dicyano- p-benzoquinone (DDQ), chloranil or o-chloranil is pref. used as oxidant.

#### REACTION CONDITIONS

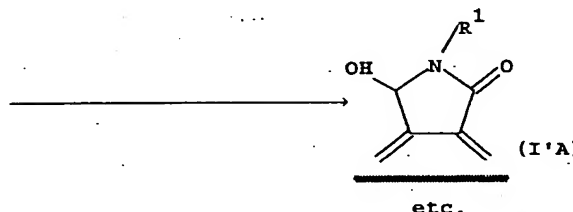
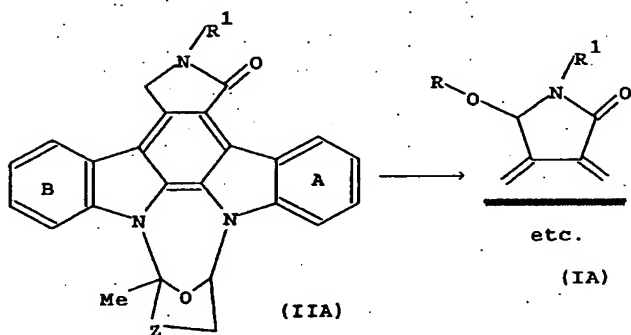
(I) is obtd. by treating (II) with 1-1.2 molar excess of the oxidant and 10-20 molar excess of 1-4C alcohol (e.g. MeOH) at 10-30°C for 2-10 hrs.

(I') is obtd. from (I) by acid hydrolysis in a mixt. of water and a water-miscible organic solvent (pref. dimethylformamide, N,N-dimethylacetamide or 1,3-dimethyl-2-imidazolinone), in the presence of strong inorganic or sulphonic acid at 40-70°C for 2-10 hrs.

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#### PROCESS

Reaction is typically as follows:



rings A and B are opt. substd.;

R<sup>1</sup> = H or lower alkyl;

Z = opt. subst. methylene or ethylene, e.g. -C(OH)(COOMe)- or -CH(OMe)-CH(NHMe)-;

R = 1-4C alkyl.

#### EXAMPLE

A soln. of 944 mg of 4'-N-(2,2,2-trichloroethoxy carbonyl) staurosporine in 10 ml dichloromethane was treated with 1 ml MeOH and 410 mg of DDQ at room temp. for 5 hours. The prod. was taken

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up in EtOAc. The organic layer was washed with satd. aq. NaHCO<sub>3</sub>, dried and evaporated to give a 7-methoxy deriv. in 96% yield.

A soln. of 14.7g of the prod. in a mixt. of 495 ml of DMF and 49.5 ml of 1N HCl was heated at 60-65°C for 3.5 hrs., then treated with 300 ml of 3% aq. ammonia. The pptd. crystals were filtered off vacuum-dried and subjected to silica gel column chromatography using CHCl<sub>3</sub> - MeOH - 25% ammonia (99:1:0.1) as eluent to give the 7-hydroxy deriv. in 85% yield. (RMH) (8pp120DwgNo.0/0)

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